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From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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in its capacity as elected Office

Date of mailing (day/month/year) 04 February 2000 (04.02.00)	
International application No. PCT/GB99/01668	**Applicant's or agent's file reference** 3.73477B GCW
International filing date (day/month/year) 26 May 1999 (26.05.99)	**Priority date** (day/month/year) 26 May 1998 (26.05.98)
Applicant O'CONNOR, Mark, James et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 December 1999 (17.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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16

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
3.73477B GCW		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01668	26/05/1999	26/05/1998
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant INSTITUTE OF MOLECULAR AND CELL BIOLOGY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/12/1999	22.08.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schwachtgen, J-L Telephone No. +49 89 2399 8933

Form PCT/IPEA/409 (cover sheet) (January 1994)

underlying problem. The technical features necessary for achieving this result have to be added.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01668

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

52	as originally filed				

Claims, No.:

1-35	as received on	03/08/2000	with letter of	02/08/2000	

Drawings, sheets:

1/15-15/15	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 5, 6, 10, 11, 30, 32
	No:	Claims	1, 7-9, 12-29, 31, 33-35
Inventive step (IS)	Yes:	Claims	2, 30, 32
	No:	Claims	1, 5-12-29, 31, 33-35
Industrial applicability (IA)	Yes:	Claims	1-12, 14, 15, 21-35
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D1: X YANG ET AL.: 'A p300/CBP-association factor that competes with the adenoviral protein E1A' NATURE., vol. 382, no. 8589, 25 July 1996 (1996-07-25), pages 319-324, XP002050400 MACMILLAN JOURNALS LTD. LONDON., GB ISSN: 0028-0836

2. The present application does not meet the requirements set forth in Article 33(2) PCT because the subject-matter of claims 1-3, 6-8, 12, 15-19, 21-26 and 28-32 is not new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT).

   D1 discloses:
   - A first isolated polypeptide spanning amino-acid residues 1805-1851 of CBP (page 320, column 1, paragraph 4; Figure 2).
   - A second isolated polypeptide consisting of the viral E1A polypeptide or consisting of the polypeptide P/CAF comprising a TRIM motif (page 322, column 1, paragraph 3; Figure 2C).
   - A method for determining whether P/CAF is capable of inhibiting the interaction between CBP and E1A or whether E1A is capable of inhibiting the interaction between CBP and P/CAF (Figure 2C).

   The CBP polypeptide disclosed in D1 comprises the TRAM consensus motif defined as SEQ ID NO. 1 in the present application. P/CAF and E1A comprise the TRIM consensus motif defined as SEQ ID NO. 10 in the present application.

   Thus, the CBP, P/CAF and E1A polypeptides *per se* anticipate the novelty of product claims 12, 21-26, 31 and 33-35, whose scope covers any compound comprising SEQ ID NO. 1 and/or SEQ ID NO. 10.

The method disclosed in D1 comprises all the process steps defined in method claims 1, 3, 4, 7-9, 13-20 and 27-29 and, thus, anticipates the novelty of said claims. Even if novelty could be established for the cited method claims, no inventive step could be recognised as the interaction of CBP/ p300 with the viral polypeptide E1A was well known in the prior art. The same applies to the subject-matter of claims 5, 6, 10 and 11 as the interaction of p53 with E6 was known.

3. The contribution of the present application over the prior art lies in the isolation of TRAM and TRIM minimal consensus polypeptide motifs (SEQ ID NO:1 and SEQ ID NO:10). Claims 2, 30 and 32, whose scope is clearly defined and encompasses neither known wild-type polypeptides comprising TRAM and TRIM motifs (e.g. CBP, p300 and E1A, E6) nor known fragments of those polypeptides, are novel.

   Furthermore, the specific TRAM and TRIM minimal consensus polypeptide motifs (SEQ ID NO:1 and SEQ ID NO:10) were not obvious in the light of the prior art. Claims 30 and 32 meet the requirements of Article 33(3) with regard to inventive step.

4. Claims 13 and 18-20, insofar as they relate to in-vivo methods, are considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item VIII

Certain observations on the international application

Claims 1, 3, 10, 13-17, 21-23, 27-29 and 31 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (i.e. a polypeptide consisting of or comprising a sequence which can bind a sequence according to SEQ ID NO. 1). This definition merely amounts to a statement of the

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	M O'CONNOR ET AL.: "Characterization of an E1A-CBP interaction defines a novel transcriptional adapter motif (TRAM) in CBP-p300" JOURNAL OF VIROLOGY., vol. 73, no. 5, May 1999 (1999-05), pages 3574-3581, XP002125824 THE AMERICAN SOCIETY FOR MICROBIOLOGY., US ISSN: 0022-538X the whole document	1-32
T	H ZIMMMERMANN ET AL.: "The human papillomavirus type 16 E6 oncoprotein can down-regulate p53 activity by targeting the transcriptional co-activator CBP7p300 " JOURNAL OF VIROLOGY., vol. 73, no. 8, August 1999 (1999-08), pages 6209-6218, XP002125825 THE AMERICAN SOCIETY FOR MICROBIOLOGY., US ISSN: 0022-538X the whole document	1-32

INTERNATIONAL SEARCH REPORT

information on patent family members

Interl. ...onal Application No
PCT/GB 99/01668

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803652 A	29-01-1998	AU 4043897 A	10-02-1998

INTERNATIONAL SEARCH REPORT

Inte. tional Application No
PCT/GB 99/01668

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C07K14/47 C07K14/475 G01N33/68 A61K38/04
C07K14/025

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 03652 A (THE GOVERNMENT OF USA) 29 January 1998 (1998-01-29) claim 27 ---	1,2
X	X YANG ET AL.: "A p300/CBP-association factor that competes with the adenoviral protein E1A" NATURE., vol. 382, no. 8589, 25 July 1996 (1996-07-25), pages 319-324, XP002050400 MACMILLAN JOURNALS LTD. LONDON., GB ISSN: 0028-0836 the whole document --- -/--	11-32

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2000	26/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Masturzo, P

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CLAIMS

1. A method for determining whether a compound is capable of inhibiting or disrupting an interaction between a first polypeptide and a second polypeptide said method comprising:

(a) (i) incubating said first polypeptide with said second polypeptide under conditions which allow the first polypeptide to bind to the second polypeptide to form a complex; and bringing the complex thus formed into contact with a candidate compound; or

(ii) incubating said first polypeptide with said second polypeptide in the presence of a candidate compound under conditions which would allow the first polypeptide to bind to the second polypeptide in the absence of the candidate compound; and

(b) determining if said candidate compound inhibits or disrupts binding of the first polypeptide to the second polypeptide;

wherein said first polypeptide comprises a TRAM sequence and said second polypeptide comprises a TRIM sequence.

2. A method according to claim 1 wherein said candidate compound is a polypeptide comprising a TRAM and/or a TRIM sequence.

3. A method according to claim 1 or 2 wherein said first polypeptide and/or said second polypeptide is a viral polypeptide.

4. A method according to claim 3 wherein said viral polypeptide is a human papillomavirus (HPV) polypeptide.

5. A method according to claim 4 wherein said HPV polypeptide is E6.

6. A method according to any one of the preceding claims wherein said first polypeptide and/or said second polypeptide is a polypeptide found in eukaryotic cells.

7. A method according to claim 6 wherein said eukaryotic polypeptide is

selected from transcription factors and cell cycle regulatory proteins.

8. A method according to claim 6 or 7 wherein said eukaryotic polypeptide is selected from mdm2, p53, TBP, E2F, YY1, CBP, p300, MyoD and TFIIB.

9. A method according to any one of the preceding claims wherein said TRAM sequence consists essentially of the sequence shown in SEQ ID NO. 1.

10. A method according to any one of the preceding claims wherein said TRIM sequence consists essentially of the sequence shown in SEQ ID NO.10.

11. Use of a compound in a method of disrupting an interaction between a first polypeptide and a second polypeptide, wherein said compound is a polypeptide comprising a TRAM sequence and/or a TRIM sequence, said first polypeptide comprises a TRAM sequence and/or said second polypeptide comprises a TRIM sequence.

12. Use of a compound in an *in vitro* method of disrupting an interaction between a first polypeptide and a second polypeptide, wherein said compound is a polypeptide comprising a TRAM sequence and/or a TRIM sequence, said first polypeptide comprises a TRAM sequence and/or said second polypeptide comprises a TRIM sequence.

13. Use of a compound in the manufacture of a medicament for use in a method of disrupting an interaction between a first polypeptide and a second polypeptide, wherein said compound is a polypeptide comprising a TRAM sequence and/or a TRIM sequence, said first polypeptide comprises a TRAM sequence and/or said second polypeptide comprises a TRIM sequence.

14. Use according to any one of claims 11 to 13 wherein said TRAM and/or TRIM sequences are as defined in claims 9 and 10, respectively.

15. Use according to any one of claims 10 to 14 wherein said first polypeptide and/or said second polypeptide are as defined in any one of claims 2 to 8.

16. Use according to any one of claims 10 to 15 wherein the disruption of said interaction inhibits viral transcription.

17. Use according to any one of claims 10 to 15 wherein the disruption of

said interaction inhibits cell cycle progression in mammalian cells.

18. Use according to claim 17 wherein said mammalian cell is a cancer cell.

19. A compound for use in a method of disrupting an interaction between a first polypeptide and a second polypeptide, wherein said compound is a polypeptide comprising a TRAM sequence and/or a TRIM sequence, said first polypeptide comprises a TRAM sequence and said second polypeptide comprises a TRIM sequence.

20. A compound according to claim 19 wherein said TRAM and/or TRIM sequences are as defined in claims 9 and 10.

21. A compound according to claim 19 or 20 wherein said first polypeptide and/or said second polypeptide are as defined in any one claims 2 to 8.

22. A compound according to any one of claims 19 to 21 wherein the disruption of said interaction inhibits viral transcription.

23. A compound according to any one of claims 19 to 21 wherein the disruption of said interaction inhibits cell cycle progression in mammalian cells.

24. A compound according to claim 23 wherein said mammalian cell is a cancer cell.

25. A method for identifying a compound which interacts with a polypeptide comprising a TRAM sequence and/or a TRIM sequence which method comprises:

(a) incubating a candidate compound with a polypeptide comprising a TRAM sequence and/or a TRIM sequence under suitable conditions; and

(b) determining if said candidate compound interacts with said polypeptide comprising a TRAM sequence and/or a TRIM sequence;

26. A method according to claim 25 wherein said compound is a polypeptide.

27. A method according to claim 25 or 26 wherein said TRAM sequence and/or said TRIM sequence is as defined in claims 9 and 10, respectively.

28. A purified polypeptide consisting essentially of a TRAM sequence.

29. A purified polypeptide consisting essentially of a TRIM sequence.

30. A polynucleotide molecule comprising a coding region encoding a polypeptide according to claim 28 or 29.

31. A polynucleotide according to claim 30 further comprising an additional coding region linked to, and in frame with, the coding region encoding a polypeptide according to claim 28 or 29.

32. A nucleic acid vector comprising a polynucleotide according to claim 30 or 31.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/11, C07K 14/47, 14/475, G01N 33/68, A61K 38/04

A2

(11) International Publication Number: WO 99/61608

(43) International Publication Date: 2 December 1999 (02.12.99)

(21) International Application Number: PCT/GB99/01668

(22) International Filing Date: 26 May 1999 (26.05.99)

(30) Priority Data:

9811303.8	26 May 1998 (26.05.98)	GB
9900157.0	5 January 1999 (05.01.99)	GB

(71) Applicant *(for all designated States except US)*: INSTITUTE OF MOLECULAR AND CELL BIOLOGY [SG/SG]; 30 Medical Drive, Singapore 117609 (SG).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: O'CONNOR, Mark, James [GB/GB]; 327 Cambridge Science Park, Milton Road, Cambridge CB4 4WG (GB). ZIMMERMANN, Holger [DE/SG]; 30 Medical Drive, Singapore 117609 (SG).

(74) Agent: WOODS, Geoffrey, Corlett; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: POLYPEPTIDES FROM CREB BINDING PROTEIN AND RELATED PROTEIN P300 FOR USE IN TRANSCRIPTIONAL REGULATION

(57) Abstract

A method for determining whether a compound inhibits or disrupts an interaction between a first polypeptide comprising a transcriptional adaptor motif (TRAM) and a second polypeptide comprising a TRAM–interaction motif. The first polypeptide and/or second polypeptide may be Mdm–2, p53, TBP, E2F, YY1, CBP/p300 or TFIIB, or a viral polypeptide such as a human papillomavirus (HPV) E6 polypeptide from HPV strain (16) or (18).

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication.where appropriate. of the relevant passages	Relevant to claim No.
X	D TROUCHE ET AL.: "The CBP co-activator stimulates E2F1-DP1 activity" NUCLEIC ACIDS RESEARCH, vol. 24, no. 21, 1 November 1996 (1996-11-01), pages 4139-4145, XP002125822 OXFORD GB the whole document ---	11-32
X	G LIANG & T HAI: "Characterization of human activating transcription factor 4, a transcriptional activator that interacts with multiple domains of cAMP-responsive element-binding (CREB)-binding protein (CBP) " JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 272, no. 38, 19 September 1997 (1997-09-19), pages 14088-24095, XP002125823 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US ISSN: 0021-9258 the whole document ---	11-32
X	CHEMICAL ABSTRACTS, vol. 127, no. 10, 8 September 1997 (1997-09-08) Columbus, Ohio, US; abstract no. 131884, V FACCHINETTI ET AL.: "Regulatory domains of the A-Myb transcription factor and its interaction with the CBP/p300 adaptor molecules" XP002125827 & BIOCHEM. J., vol. 324, no. 3, 1997, pages 729-736, ISSN: 0950-9232 abstract ---	11-32
A	File Medline, abstract 97154536, 1997 XP002125826 & V SARTORELLI ET AL.: "Molecular mechanisms of myogenic coactivation by p300; direct interaction with the activation domain of MyoD and with the MADS box of MEF2C" MOLECULAR AND CELLULAR BIOLOGY, vol. 17, no. 2, February 1997 (1997-02), pages 1010-1016, abstract --- -/--	1-32